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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,867	04/16/2004	Jason W. Chin	54A-000240US	8312

22798 7590 03/19/2008

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	PAPER NUMBER
1656	
MAIL DATE	DELIVERY MODE
03/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,867	CHIN ET AL.	
	Examiner	Art Unit	
	KAGNEW H. GEBREYESUS	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,39,41,42,47,50-57,131-133 and 139-151* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,39,41,42,47,50-57,131-133 and 139-151* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants reply on November 13, 2007 and further on December 17, 2007 to the Office action mailed on May 09, 2007 is acknowledged. Claims 38, 39, 42, 47, 131, 133 are amended. Claims 139-151 are new claims. Claims 40, 43-46 are cancelled. Claims 38, 39, 41-42, 47, 50-57, 131-133 and 139-151 are present for examination.

Withdrawn- Objection to Specification

The disclosure was objected to because it contains an embedded hyperlink and/or other form of browser-executable code in paragraphs [0184] and [0294]. Furthermore the specification was objected to for an unclear incorporation by reference. These objections are withdrawn by virtue of Applicants amendments.

Withdrawn -Claim Objections

Claims 38-57 and 131-133 were objected to for the recitation "at least one unnatural amino acid" and the term "at least one post-translational modification." This rejection is withdrawn by virtue of Applicants amendments to the claims.

Withdrawn - Claim Rejections - 35 USC § 112

Claims 48 and 49 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is withdrawn because claims 48

and 49 have been cancelled by Applicant.

Claim Rejections - 35 USC § 112

Claims 38, 39, 41, 42, 47, 50-57, 131-133, and now including claims 139-143, and 146-151 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a Gal4 protein with one or two unnatural amino acids (see for example figs. 1, 3 for Gal 4), it does not reasonably provide enablement for a recombinant protein comprising any number (up to 100%) of unnatural amino acids. Furthermore the specification is not enabled for any recombinant protein comprising any number of unnatural amino acids or keto amino acids that are further modified post translationally.

The response argues:

> With respect to claim 38, the rejection argued that it was unclear which amino acids and what percentage of the relevant GAL4 could be modified. The claims have been modified to expressly recite that the relevant GAL4 mutants are at least 60% identical to a wild-type GAL4 protein comprising a DNA binding domain and an activation domain.

Claims 38 now recites "…a recombinant Gal4 protein or portion thereof, in a eukaryotic cell , comprising at least one unnatural amino acid, and wherein the Gal4 protein, or portion thereof is at least 60% identical to a Gal4 protein …capable of activating a Gal4 responsive gene…"

However these claims are so broad as to encompass a Gal4 protein where any number of unnatural amino acids are incorporated. The Gal4 protein has a length of 881 amino acid, thus a variation of up to 40% comprises any possible modification which

includes deleting, adding or substituting up to 352 amino acids with unnatural amino acids or natural amino acids or combinations thereof. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants broadly encompassed in the claims. Although the structure and functional domains of the Gal4 protein are well known (such as the DNA binding domain and the activation domain), the specification does not provide guidance with regards to the extent of unnatural amino acids modification that these functional domains can tolerate while retaining activity. The specification teaches incorporation of one or two unnatural amino acids in specific sites in the DNA binding domain (see fig. 3A and 3B) wherein said DNA binding domain retains its activity. However the specification does not provide teaching and guidance with regards to the activity of this domain if it comprises 3, 4…10 or more unnatural amino acids. Thus the activity of such a protein is entirely unpredictable.

Furthermore while recombinant and mutagenesis techniques are known, it is not routine in the art to produce functional proteins wherein multiple substitutions or multiple modifications, with unnatural amino acids are made as encompassed in claims 39, 41, 42, 47, 50-57, 131-133, 139-143, and 146-151.

Claims 139-143 are rejected because of these claims recite a Gal4 protein having 70%-90% identity to a wild type Gal4 protein from *Saccharomyces cerevisiae* thus encompass incorporation 80 or more unnatural amino acids into the Gal4 protein (90%). A recombinant Gal4 protein showing 90% sequence identity to a wild type Gal4 protein can encompass incorporation of up to 83 unnatural amino acids in the DNA

binding domain or in the DNA activation domain. The specification provides 1 or 2 substitutions in the DNA binding domain of the Gal4 protein. The function of a protein comprising 80 or more unnatural amino acids in a Gal4 protein will be unpredictable.

Claims 146 and 147 are rejected because these claims are drawn to Gal4 proteins comprising undefined number of mutations in either the DNA activation domain (146) or in the DNA binding domain (147).

. Furthermore the positions within a protein's sequence where unnatural amino acid modifications can be made with a reasonable expectation of success for obtaining the desired activity/utility are limited for any protein (see specification for example figures 3 and 5 which show that not all amino acid positions can be replaced with unnatural amino acids and retain function of the Gal4 protein). Therefore the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. substitutions with unnatural amino acids at multiple positions.

Therefore the specification does not support the broad scope of the claims which encompasses all modifications and fragments of any recombinant mutant Gal4 protein with up to 60% identity to wild type Gal4, or the broad scope of claims 39, 41 and 149-150 that encompass any recombinant protein comprising any number of keto unnatural amino acids (or 5 to 10 keto unnatural amino acids (claims 149-150)) and any post-translational modifications with saccharide moieties wherein said modified protein further comprises any oligosaccharide covalently coupled to an asparagine, threonine or serine residue of said recombinant protein. Furthermore claims 42, 47, 50-57, 131-133

encompass any protein comprising any type and number of unnatural amino acids that are further modified by various types of post-translational modifications. However the specification does not teach how to make or use such proteins by a disclosure of specific ORS/OtRNA molecules required for incorporating specific unnatural amino acids into said recombinant proteins. In summary, the specification does **not** establish: (A) the extent of modification and the regions of the protein structure which may be modified without effecting function; (B) the general tolerance of the specific protein to modification with multiple unnatural amino acids and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in a protein with an expectation of preserving the desired biological function; and (D) guidance as to which of the essentially infinite possible recombinant proteins or compositions thereof comprising unnatural amino acids and posttranslational modifications is likely to be made and be used.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a composition comprising a recombinant Gal4 protein, or portion thereof in a eukaryotic cell, comprising undefined number of unnatural amino acids (claims 38-42, 47, 50-57, 131-133 139-148), and wherein the GAL4 protein, or portion thereof is at least 60%-90% identical to a wild type GAL4 protein of *Saccharomyces cerevisiae* or with more than two unnatural amino acids (claims 149 and 150), and wherein the recombinant mutant GAL4 protein retains function.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any protein comprising any number of unnatural amino acids having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicant's argument with regards to the previous rejection of claims 38-57 and 131-133 has been carefully considered.

Applicants argue:

"With respect to claim 38, the rejection argued that it was unclear which amino acids and what percentage of the relevant GAL4 could be modified. The claims have been modified to expressly recite that the relevant GAL4 mutants are at least 60% identical to a wild-type GAL4 protein comprising a DNA binding domain and an activation domain. Further, Applicants point out that GAL4 is one of the most completely studied proteins in modem molecular biology--the precise crystal structure for the protein is known, the DNA binding and activation domains are well-characterized, and the protein is routinely used as a reporter gene, making it amenable to super-high throughput activity screening. Accordingly, it is reasonable for one of skill to routinely modify this protein using the orthogonal systems of the invention, particularly when high throughput systems for screening for GAL4 activity are in such wide-spread use".

However although the DNA binding domain and the activation domain of Gal4 are well characterized, the tolerance of modification to the Gal4 protein depends on the region where said modification is made. For example, figure 3 of Applicants own specification teaches that even single mutations in the DNA binding domain of the Gal4 protein can render Gal4 inactive. Among the few functional Gal4 variants the double

mutant comprising a T44 and R110 mutation are clearly functional while a plethora of other double and single mutants are non-functional. Therefore the guidance provided in Applicants own specification argues against the claimed scope encompassed.

New grounds of rejection necessitated by amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 148 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 148 recites the limitation "the keto amino acid" referring to claim 38. There is insufficient antecedent basis for this limitation in the claim. Claim 38 does not specifically recite a keto amino acid.

Withdrawn -Claim Rejections - 35 USC § 102

Claims 39-42, 45-57 and 131-133 were rejected under 35 U.S.C. 102(e) as being anticipated by Schultz et al (US 7,129,333 B2) which claims priority from U.S. provisional patent application Ser. No. 60/419,265, filed Oct. 16, 2002.

Claims 38 and 131 were rejected under 35 U.S.C. 102(b) as being anticipated by Kiga et al.

Claims 38 and 131 were rejected under 35 U.S.C. 102(a) as being anticipated by

Sakamoto et al. Clam 132 was rejected under 35 U.S.C. 102(b) as being anticipated by Gallivan et al.

Claim 131 was rejected under 35 U.S.C. 102(b) as being anticipated by Ellman et al (Science, 1992, vol. 255, 197-200).

The above rejections are withdrawn following Applicants' amendment that adds further limitations to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 39, 41-42, 47, 131-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al (US 20050186657 A1 now US 7,129,333 B2). Schultz et al teach compositions comprising a protein (glycoprotein) wherein at least one unnatural amino acid such as para-acetyl-L-phenylalanine (a keto-amino acid) is incorporated into

said protein and which is further modified with saccharide moieties. Schultz et al teach that in order for a eukaryotic system to be used, the vectors optionally comprise generic expression cassettes containing at least one independent terminator sequence, sequences permitting replication of the cassette in eukaryotes, or prokaryotes, or both (e.g., shuttle vectors) and selection markers for both prokaryotic and eukaryotic systems. Claims 39, 41-42, 131-133 are obvious over Schultz et al because they teach glycoprotein mimetics produced by incorporating a p-acetyl-phenylalanine that is further post-translationally modified with saccharide moieties.

Schultz et al do not teach a composition where comprising a protein wherein the modification is selected from the group consisting of: phosphorylation, lipid-modification, palmitovlation, palmitate addition and a glicolipid-linkage modification. However, it would have been obvious for a person of ordinary skill in the art to produce any naturally occurring eukaryotic protein comprising the above naturally occurring modifications in a purified form as suggested by Schultz et al in column 60 lines 56-63. .

One of skill in the art would have a reasonable expectation of success because post-translational modifications are normal physiological processes in eukaryotic cells.

This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kagnew H Gebreyesus PhD/
Examiner, Art Unit 1656
/K. H. G./

/Kathleen Kerr Bragdon/
Supervisory Patent Examiner, Art Unit 1656